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AF/1631 FW 4

PTO/SB/21 (09-04)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	09/753,869
Filing Date	January 3, 2001
First Named Inventor	Richard H. Griffey
Art Unit	1631
Examiner Name	Michael L. Borin
Attorney Docket Number	IBIS0036-101 (IBIS-0005US.C1)

ENCLOSURES ***(check all that apply)***

- ☒ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment / Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
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  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below)*:
  1. Duplicate copies of Appeal Brief
  2. Return Card

Remarks **Express Mail Label No.: EV 513562913 US**
Date of Deposit: 24 November 2004

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm	Cozen O'Connor		
Signature	Paul K. Legaard		
Printed Name	Paul K. Legaard		
Date	24 November 2004	Reg. No.	38,534

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FEE TRANSMITTAL for FY 2005

Effective 10/01/2004. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 340

Complete if Known	
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METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 50-1275

Deposit Account Name: Cozen O'Connor

The Director is authorized to: *(check all that apply)*
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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	790	2001	395	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below		Fee Paid
Total Claims		- ** =	0	X		=	0
Independent Claims		- ** =	0	X		=	0
Multiple Dependent				X		=	0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	88	2201	44	Independent claims in excess of 3
1203	300	2203	150	Multiple dependent claim, if not paid
1204	88	2204	44	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

**or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	430	2252	215	Extension for reply within second month	
1253	980	2253	490	Extension for reply within third month	
1254	1,530	2254	765	Extension for reply within fourth month	
1255	2,080	2255	1,040	Extension for reply within fifth month	
1401	340	2401	170	Notice of Appeal	
1402	340	2402	170	Filing a brief in support of an appeal	340
1403	300	2403	150	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,370	2453	685	Petition to revive – unintentional	
1501	1,370	2501	685	Utility issue fee (or reissue)	
1502	490	2502	245	Design issue fee	
1503	660	2503	330	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 340

SUBMITTED BY					Complete *(if applicable)*
Name (Print/Type)	Paul K. Legaard	*Registration No. (Attorney/Agent)*	38,534	*Telephone*	(215) 665-6914
Signature				*Date*	24 November 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of: **Richard H. Griffey and Eric E. Swayze**

Confirmation No: **1982**

Serial No.: **09/753,869** Group Art Unit: **1631**

Filed: **January 3, 2001** Examiner: **Michael L. Borin**

Title: **A Method Of Identifying *In Silico* Each Compound Of A Virtual Library**

EXPRESS MAIL INFORMATION

EXPRESS MAIL LABEL NO: EV 513562913 US

DATE OF DEPOSIT: 24 November 2004

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Alexandria, VA 22313-1450

APPELLANT'S APPEAL BRIEF PURSUANT TO 37 CFR §1.192

Appellants hereby submit an original and two copies of the present Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Rejection dated May 28, 2004 in connection with the above-identified application. An Amendment and Request for Reconsideration amending claim 27 was filed August 25, 2004. An Advisory Action dated September 15, 2004 was received by Applicants. A Notice of Appeal was timely filed September 27, 2004.

I. Real Party In Interest

The real party in interest in the above-identified patent application is Isis Pharmaceuticals, Inc., a corporation of Delaware. An Assignment to Isis Pharmaceuticals, Inc. was recorded at Reel 012121, Frame 0770 on August 30, 2001.

II. Related Appeals And Interferences

Appellants' undersigned attorney is unaware of any related appeal or interference that will affect or be affected by or have any bearing on the decision rendered in this appeal.

III. Status Of Claims

Claims 12 and 27-29 remain pending and are now on appeal -- the appealed claims appear in Appendix A.

IV. Status Of Amendments

Claim 27 was amended in response to the Final Rejection. The Advisory Action indicated that the amendment to claim 27, which overcame the rejection under 35 U.S.C. §112, second paragraph, was entered into the record.

V. Summary Of The Invention

Appellants' claimed invention relates to methods of identifying *in silico* each compound of a virtual library of compounds. The compounds are dissected into constituent fragments, wherein each of the constituent fragment is associated with at least one reagent. The reagent represents a chemical necessary to introduce the constituent fragment into the compound. The dissecting is based on the ease of synthesis of the compound from the constituent fragments. The constituent fragments are then added together in sequential synthesis rounds defining thereby a synthetic method for the compound from the constituent fragments. The virtual synthetic addition of constituent fragments of the compounds are tracked according to the synthetic method for the compound, thereby identifying each compound of the virtual library. The dissecting can be further based on commercial availability of reagents. The method synthetic method for the compound can use known reactions and reagents. The dissecting can be characterized by formation of constituent fragments for which the reverse transformation is known.

VI. Issues

Two issues remain for resolution in this appeal and include:

1) whether claims 12 and 27-29 are unpatentable under 35 U.S.C. §103(a) as allegedly being obvious in view of Walters et al., Drug Discovery Today, 1998, 3(4), 160-178 (hereinafter, the "Walters reference"); and

2) whether claim 12 is unpatentable under the doctrine of obviousness-type double patenting over claims 8 and 9 of U.S. Patent No. 6,253,168 (hereinafter, the "'168 patent").

VII. Grouping of the Claims

For issue 1 identified above, Appellants believe that claims 12 and 27-29 stand or fall together.

VIII. Arguments

A. The Claimed Invention Is Not Obvious Over The Walters Reference (Issue 1)

The rejection of claims 12 and 27-29 under 35 U.S.C. §103(a) over the Walters reference is improper and should be reversed because the Walters reference does not teach every feature recited in the claims.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Significantly, the Walters reference does not teach or suggest all the features recited in Appellants' claims.

The Examiner asserts that the Walters reference teaches "presenting components of the virtual library as combination of reagents and corresponding reactions" and evaluating "members of the library by their synthesizability," and, thus, it would have been "obvious to one skilled in the art to characterized any compound of interest, and thus to extend, if needed, such

characterization to each compound of the library" (see, Office Action dated December 30, 2003). Appellants submit that the Examiner's characterization of the Walters reference is misplaced.

Claim 12 recites, in part, that the compounds of the virtual library are dissected into their constituent fragments and the subsequent virtual synthetic addition of these fragments is tracked. The Walters reference does not teach or suggest dissecting the compounds of a virtual library into their constituent fragments, where the constituent fragment is associated with at least one reagent that represents a necessary chemical to introduce the constituent fragment into the compound, and where the dissecting is based on the ease of synthesis of the compound from the constituent fragments, let alone track the virtual synthetic addition. Rather, the Walters reference reviews the state of the art in virtual screening and reports the many problems associated therewith. In particular, the Walters reference primarily deals with the construction and screening of virtual libraries.

The only portion of the Walters reference explicitly referred to by the Examiner is Figure 1 on page 161. The Examiner asserts that Figure 1 is seen as "representation of member of a compound library dissected into fragments and presented as a synthetic round leading to the target compound." Figure 1 of the Walters reference, however, is described by the authors of the Walters reference at page 160:

> There are perhaps millions of chemical 'libraries' that a trained chemist could reasonably hope to synthesize. Each library can, in principle, contain a huge number of compounds – easily billions. Combinatorial chemists have already demonstrated, in several prototype systems, that libraries containing 1,000-100,000 compounds can in fact be assembled. Figures 1-3 give simple examples that have appeared in the literature recently. In Figure 1, 1,4-benzodiazepine scaffold is shown, along with the components from which this scaffold might be assembled. In the same fashion, Figure 2 shows a pyrrolidine library and Figure 3 shows an acylpiperidine library. The 'building blocks' are in many cases very simple and can readily be purchased or synthesized. In each of these three examples, it can easily be imagined that the library could contain 10^9 or more possible compounds. A reasonable conclusion from the preceding analysis is that a 'virtual chemistry space' exists that contains perhaps 10^{100} possible molecules (Box 1). (citations omitted)

Thus, quite clearly, the authors are referring to Figure 1 to provide an example of "building blocks" (i.e, components) from which a scaffold could be assembled. Thus, this portion of the

Walters reference amounts to nothing more than a combinatorial method for building a scaffold from "building blocks." Nowhere does this portion of the Walters reference teach or suggest dissecting compounds (as opposed to building scaffolds from "building blocks") into constituent fragments, where the constituent fragment is associated with at least one reagent that represents a necessary chemical to introduce the constituent fragment into the compound, and where the dissecting is based on the ease of synthesis of the compound from the constituent fragments.

The Examiner refers to a "chemically aware builder" that is alleged to comprise "presenting components of the virtual library as combination of reagents and corresponding reactions" and further asserts that the compounds generated thereby are "defined by synthetic rounds between its chemical components" (see, page 3 of the Office Action dated December 30, 2003). The Examiner, however, does not explicitly point out where such a teaching is present in the Walters reference. The only portion of the Walters reference that refers to a "chemically aware builder" that Appellants are able to locate is Figure 13 on page 169. The Walters reference refers to Figure 13 on page 168 as follows:

> Working in the forward direction – limiting the compounds constructed – seems to be the more straightforward approach to implement and provides a natural fit with current thinking about the assembly of real combinatorial libraries. Construction of a library on the computer uses a set of 'allowed' building blocks and reactions, such as is given in Figure 13. A limit can be placed on the number of building blocks that are allowed in any molecule – for example, no more than four building blocks assembled from three reactions. The library of building blocks can also be limited to those that are either commercially available or readily and cheaply synthesized. Ideally, such molecule-building programs should apply detailed knowledge of cross-reactivity (i.e., functional groups that are not compatible) to help eliminate molecules that could not be readily synthesized in practice. These programs, such as CONJURE are capable of processing hundreds of thousands of compounds per hour on a single workstation.

Thus, the "chemically aware builder" that the Walters reference refers to is one which limits the kinds of compounds that are constructed by limiting the number and type of building blocks and reactions used. This portion of the Walters reference fails to teach or suggest that the virtual synthetic addition of constituent fragments of the compounds according to the synthetic method for the compound is tracked in any manner. Indeed, Appellants' specification teaches tracking

the virtual synthetic addition of the constituent fragments (i.e., accounting for the fragments being introduced, the related transformations or reactions associated with the fragments, and the alternate transformations that lead to the introduction of a common fragment into the desired compounds) at, for example, page 14, line 23 to page 15, line 8, and page 17, line 27 to page 28, line 7 of the specification.

The Examiner also refers to "Computer-Aided Estimation of Synthetic Accessibility" stating that such software "evaluates members of the library by their synthesizability" (see, page 3 of the Office Action dated December 30, 2003). Again, the Examiner does not explicitly point out where such a teaching is present in the Walters reference. The only portion of the Walters reference that refers to a "Computer-Aided Estimation of Synthetic Accessibility" that Appellants are able to locate is on page 169. The Walters reference refers to "Computer-Aided Estimation of Synthetic Accessibility" on page 169 as follows:

> Johnson and coworkers have adopted the CAOS [computer-aided organic synthesis] paradigm into the high-throughput world with a program called CAESA (Computer-Aided Estimation of Synthetic Accessibility) that is designed to rank the synthesizability of a series of candidate molecules generated by a *de novo* design program. CAESA uses a library of generalized synthetic transformations in conjunction with an analysis of features such as stereocenters to determine which molecules can be easily synthesized.

Again, this portion of the Walters reference fails to teach or suggest that the virtual synthetic addition of constituent fragments of the compounds according to the synthetic method for the compound is tracked in any manner.

Thus, the prior art reference (the Walters reference) does not teach or suggest all the features recited in the claims. Although the Walters reference reports an overview of virtual screening of compounds, and also reports the existence of computer software for carrying out particular functions, the Walters reference fails to teach or suggest a method of identifying *in silico* each compound of a virtual library of compounds wherein the compounds are dissected into constituent fragments, where the constituent fragment is associated with at least one reagent that represents a necessary chemical to introduce the constituent fragment into the compound, and where the dissecting is based on the ease of synthesis of the compound from the constituent fragments, adding the constituent fragments together in sequential synthesis rounds defining

thereby a synthetic method for the compound from the constituent fragments, and tracking the virtual synthetic addition of constituent fragments of the compounds. Thus, the claimed invention is not obvious in view of the Walters reference.

In view of the foregoing, Appellants respectfully request that the rejection of claims 12 and 27-29 under 35 U.S.C. §103(a) over the combination of the Walters reference be reversed.

B. The Claimed Invention Is Not An Obvious Variant (Issue 2)

The rejection of claim 12 under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 8 and 9 of U.S. Patent No. 6,253,168 (hereinafter, the "'168 patent") is improper and should be reversed because the claimed invention is not an obvious variant of the subject matter recited in claims 8 and 9 of the '168 patent.

An obviousness-type double patenting rejection is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. §103. *In re Braithwaite*, 154 U.S.P.Q. 29, 34 (C.C.P.A. 1967) and *In re Longi*, 225 U.S.P.Q. 645, 648 n.4 (Fed. Cir. 1985). Thus, under the law, the pivotal question in an obviousness-type double patenting analysis is: Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent? *In re Vogel*, 164 U.S.P.Q. 619 (C.C.P.A. 1970). If the answer to this question is no, there can be no double patenting. In making this analysis, then, the proper inquiry is as taught in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). See, M.P.E.P. §804. No such analysis is even attempted by the Examiner.

For the record, claims 8 and 9 of the '168 patents read as follows:

> 8. A method of generating a database comprising information about the member compounds of a virtual library of compounds comprising:
>
> selecting each of said compounds for said virtual library and, for each, dissecting each of said compounds into fragments;
>
> linking together the fragments of each of the compounds;
>
> tracking the sequence of linkage for each compound;
>
> grouping two or more compounds of said library together to form a mixture;

grouping a further two or more compounds of said library together to form a further mixture;

linking together the tracked information of each of the members of said mixture;

linking together the tracked information of each of the members of said further mixture; and

storing said tracked information thereby generating a database.

9. A method of generating a database comprising information about member compounds in a virtual library of compounds comprising:

selecting each of said compounds for said virtual library and, for each, dissecting said compounds into fragments;

representing each of said fragments as a transformation wherein each transformation is a one to one link between a fragment and a reagent used to introduce said fragment into one of said compounds;

linking together the transformations of each of the compounds;

tracking the sequence of linkage for each compound; and

storing said transformation information thereby generating a database.

The only remarks of record by the Examiner are 1) "generating the database information as claimed in '168 will, therefore, obviously describe (identify) the member compound; further, the methods steps of the instant and referenced claims are the same" (see, page 5 of the Office Action dated December 30, 2003); and 2) "it would be obvious to an artisan that information obtained by generating the database information as claimed in the reference will serve as a descriptor and identifier of a target compound" (see, page 6 of the Final Rejection dated May 28, 2004).

Clearly this limited "analysis" is not sufficient under *Graham v. John Deere Co.* In addition, the methods steps recited in claim 12 of the present application and the method steps of claims 8 and 9 of the '168 patent are clearly not the same. Indeed, there is no recitation of, for example, "where the dissecting is based on the ease of synthesis of the compound from the constituent fragments" in either claim 8 or claim 9 of the '168 patent. Further, the Examiner in

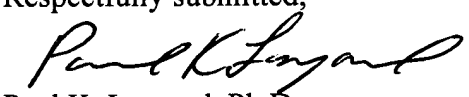
the present application has restricted "Claims 12, 13, drawn to method of identifying compounds" from "Claims 14-26, drawn to method of storing information" (see, Restriction requirement dated May 20, 2002). Clearly, methods of "generating a database comprising information about the member compounds of a virtual library of compounds" (see preamble of claim 8 of the '168 patent) and "generating a database comprising information about member compounds in a virtual library of compounds" (see preamble of claim 9 of the '168 patent) are, indeed, methods of "storing information," which have been restricted out of the present application. Thus, the Examiner has failed to establish a *prima facie* case of obviousness-type double patenting in view of the foregoing comments.

In view of the foregoing, Appellants respectfully request that the rejection of claim 12 under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 8 and 9 of '168 patent be reversed.

IX. Conclusion

All rejections of the pending claims are improper and should be reversed. For the reasons given above, appealed claims 12 and 27-29 are patentable.

Respectfully submitted,



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Appendix A

Claims on Appeal

The following claims are on appeal:

12. A method of identifying *in silico* each compound of a virtual library of compounds comprising:

dissecting said compounds into constituent fragments, where the constituent fragment is associated with at least one reagent, which represents a necessary chemical to introduce the constituent fragment into the compound, and where the dissecting is based on the ease of synthesis of the compound from the constituent fragments;

adding said constituent fragments together in sequential synthesis rounds defining thereby a synthetic method for the compound from the constituent fragments; and

tracking the virtual synthetic addition of constituent fragments of said compounds according to the synthetic method for the compound, thereby identifying each compound of the virtual library.

27. The method according to claim 12 wherein the dissecting is further based on commercial availability of reagents.

28. The method according to claim 12 wherein the synthetic method for the compound uses known reactions and reagents.

29. The method according to claim 12 wherein the dissecting is characterized by formation of constituent fragments for which the reverse transformation is known.